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(57) Abstract

A drug delivery system processed via thermoform techniques, having rapid, active agent release properties that are useful in pharmaceutical dosage forms. The delivery system may be utilized as particles that contain active agents and solubilizing agents and which are contained in a dosage form.

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IMMEDIATE RELEASE DRUG DELIVERY FORMS

This application is a continuation-in-part of Serial No. 08/946,070, filed October 7, 1997.

Field of the Invention

The invention deals with an active agent delivery system that has rapid release properties for active agents that are not normally readily water-soluble, methods of making the delivery system and products made therefrom. The fast release of the active agents from pharmaceutical dosage forms is achieved by thermoforming the active along with a solubilizing agent prior to forming the dosage form.

Background of the Invention

Melt-blended formulations containing active agents and solubilizers are known in the art.

U. S. Patent 4,944,949 discloses dissolving, or co-melting non-steroidal anti-inflammatory drugs (NSAIDs) in melts of nonionic surfactants such as poloxamers (col. 5, line 31) to form micelles. Micelles are aggregates in which surfactant molecules are arranged in a spheroidal structure, with the hydrophobic regions at the core and the hydrophilic regions at the other surfaces. Drug:surfactant ratios of 1:5.7 to 1:50 are disclosed at column 12, line 57.

U. S. Patent 5,281,420 shows tebufelone, an anti-inflammatory agent, in solid dispersions containing 15% to 75% tebufelone, 25% to 65% of a poloxamer surfactant (col. 1, lines 35-51) and other ingredients.

U. S. Patent 5,525,355 deals with laxative compositions that contain poloxamer surfactants, as stool softeners, melt-blended with stimulants. The ratio of surfactant to stimulant is 2:1 to 20:1 (col. 2, line 22+). The compositions are administered in hard gelatin capsules.

EPO Application 0 317 780, published May 31, 1989, shows quick-release and sustained-release formulations containing dihydropyridine calcium channel blockers, poloxamer surfactants and other ingredients. The quick release compositions contain 0.15:1 to 0.5:1 of the water-soluble cellulosic derivative hydroxypropylmethylcellulose to a poloxamer/dihydropyridine complex (p. 6, l. 48-49). The complex contains 1:1 to 1:10 ratios of drug to surfactant (page 6, lines 25-27).

WO97/02017, published January 23, 1997, discusses oral dosage forms that contain a solid dispersion of an active ingredient in a poloxamer polymer formed by solvent dissolution and melt-blending. The ratio of active agent to poloxamer is 0.1:1.0 to 10.0:1.0 (page 3, line 280.

U.S. 4,727,109 shows liquid preparations containing an active agent and a carrier system consisting of a hydrophilic component, a hydrophobic component and a solubilizer. The hydrophilic component may be a polyethylene glycol or a polyoxyethylene/polyoxypropylene copolymer. See column 2, lines 35-44.

U.S. 5,456,923 describes solid dispersions of drugs in polymers made by extruding the two materials and pulverizing the extrudate. Polyoxyethylene/polyoxypropylene copolymers are disclosed, at column 3, lines 33-4, for use with the polymers as plasticizers.

U.S. 5,292,461 deals with pellets produced by spraying an active agent with a wetting agent. Polyethylene glycols are disclosed as lubricants (col. 7, l. 62) and agents that influence the release of the active ingredient (col. 8, l. 1-2). Poloxamers are recited as surface-active agents (col. 7, l. 65).

Summary of the Invention

The present invention is a thermoformed drug delivery system useful in making dosage forms having improved dissolution and shorter T_{max} for the drug consisting essentially of from about 50% to about 80% of an undissolved solid particulate form of at least one active agent in intimate contact with from about 20% to about 50% of a polymeric solubilizing agent wherein the solid particulate active agent is generally soluble in a melt of the polymeric solubilizing agent.

Preferably the solubilizing agent is a diblock copolymer containing polyoxyethylene and polyoxypropylene units. More preferably the solubilizing agent is Poloxamer 188.

The active agent of the drug delivery system can be any drug that could benefit from the improved release properties of the present invention and which is normally soluble, or dissolvable in a melt of the polymeric solubilizer. Preferably the drug is selected from the group consisting of H_2-antagonists, non-narcotic analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), anti-cholesterolemics, anti-allergy agents, anti-migraine agents and combinations thereof. Most preferably the active agent is ibuprofen.

Detailed Description of the Invention

Fast release dosage forms include those in which T_{max}, or time to maximum plasma drug concentration for the delivered drug or drug delivery form, is shortened. By "shorter T_{max}" or "shortened T_{max}" applicants refer to enhanced absorption of active agent(s) at earlier time points than would be found using conventional forms of, or delivery vehicles for, the drug. The product of the invention can generally release at least 80% of the active agent(s) in about 5 minutes or less in the appropriate pH environment.

The invention can utilize any appropriate processing techniques to make the drug delivery material, including liquiflash and extrusion processes. The drug delivery material comprises solid particles of active agent(s) in intimate contact with, embedded in, or at least partially encapsulated or enveloped by a polymeric solubilizing agent or combinations thereof, a melt of which would normally solubilize, or dissolve the active. The inventive material may then be processed into particles which in turn can be processed into conventional capsules or tablets or other dosage forms, all of which will exhibit fast release properties of the active. Oral dosage forms are typical.

One aspect of the invention is directed to drug delivery products made by subjecting at least one active agent and a solubilizing agent to thermoform processing to form a drug delivery system.

By thermoform, thermoforming, or thermoform processing the applicants mean a process that exposes the active and the solubilizing agent to only sufficient amounts of heat, or other energy, such that the majority of active does not co-melt and mingle with the solubilizing agent, or dissolve in the solubilizing agent (melt-blend), or otherwise form a single phase with the solubilizing agent, when the solubilizing agent forms a liquid, or liquiflash phase. An important aspect of thermoform processing is the control of the tendency of the solubilizer and the active agent to combine into a single phase or dispersion during the heating process. In the thermoformed delivery system the solubilizing agent should at least partially encapsulate, envelop or otherwise be in intimate contact with, solid particles of the active agent. Co-melts, or solid solutions of the active and solubilizing agent(s) are to be minimized and avoided as much as possible. It is believed that such forms interfere with the rapid release properties of the present invention. Solid particles of the active which have recrystallized from a co-melt of the active and solubilizer are also to be minimized.

Liquiflash processing is one thermoform process that is known in the art and useful in the practice of this invention. Liquiflash processing is disclosed, for example, in U.S. Patent 5,683,720, issued November 4, 1997. U.S. Patents 5,445,769 and 5,458,823, as well as U.S. Patent Application, Serial No. 08/874,215, filed June 13, 1997 disclose some devices that can be utilized to make the inventive thermoformed delivery products by means of liquiflash processing.

In addition to liquiflash processing, extrusion processes or other methods which will not co-melt (melt-blend) the solubilizer and the active agent to any significant degree can be utilized for the practice of the present invention.

Compositions that are useful in the invention are feedstocks that contain:

(a) about 50% to about 80% of solid particles of at least one active ingredient or agent; and

(b) about 50% to about 20% of a solubilizing agent.

The active ingredients useful herein can be selected from a large group of therapeutic agents. Mixtures and pharmaceutically acceptable salts of these agents may also be used.

Active agents that are sparingly soluble in biological fluids (e.g., water) are examples of solid active agents whose dissolution and release properties are particularly enhanced by the delivery system described herein. These agents include, analgesics, including non-steroidal anti-inflammatory drugs (NSAIDs).

Analgesics include, for example, non-narcotic analgesics such as aspirin, acetaminophen, acetaminophen plus caffeine, NSAIDs.

Useful NSAIDs include ibuprofen; diclofenac and its alkali metal salts; fenoprofen and its metal salts; ketoprofen, naproxen and its alkali metal salts; and piroxicam and its salts.

Combinations of various types of drugs in addition to analgesics, as well as combinations of individual drugs, are contemplated. In particular, combinations containing non-narcotic analgesics and non-toxic antagonists for the N-methyl-D-aspartate receptor, *e.g.* a morphinan such as dextromethorphan or dextrorphan, or a nontoxic substance that blocks a major intracellular consequence of N-methyl-D-aspartate receptor activation, such as a ganglioside are contemplated herein.

The solubilizing agents, or solubilizers, used herein are commercially available solubilizers such as generally solid diblock copolymers containing only polyoxyethylene units and polyoxypropylene units. Poloxamers containing polyoxyethylene and polyoxypropylene block segments are particularly useful, with those having about 60% to about 90%, and particularly those having about 70% to about 80%, polyoxyethylene units being notable. Suitable polymers are sold using "Lutrol," "Monolan" and "Pluronic" trade names (BASF manufacturer). Poloxamer 188 (Pluronic F68) is especially effective. This diblock copolymer surfactant has an average molecular weight of about 7680 to 9510. See Handbook of Pharmaceutical Excipients (2nd Edition), 1994, pages 352-354. Other useful "Pluronic" polymers include those designated as F87, F108, F127 and F237.

Another group of useful solubilizers is polyethylene glycol esters sold as "Gelucire" (Gattefosse). "Gelucire 50/13" is a polyethylene glycol-32 glyceryl palmitostearate (HLB 13).

Solid particles formed from the inventive delivery system may optionally be coated with one or more pharmaceutical coatings after their formation. However, any coating should not significantly alter the fast release properties of the particles or dosage forms, *e.g.,* tablets, in which they are used. Useful coatings include aesthetic coatings, taste-masking coatings, enteric coatings and others conventionally used in the pharmaceutical field. Coatings will be present in amounts consistent with their functions--*i.e.* in suitable pharmaceutical amounts.

Suitable amounts and types of pharmaceutical excipients, *e.g.,* fillers, flavors, flow control agents, lubricants, diluents and the like, such as shown below in Table 1, may be blended with particles of the delivery systems before or during the preparation of suitable dosage forms. Such excipients are not combined, however, with the feedstock material of the delivery system prior to the thermoform processes. The excipients or combinations thereof may separately be subjected to thermoform processing, but they are not processed in the presence of the active/solubilizing agent delivery system feedstock.

Solid diluents are a typical excipient useful in the formation of typical dosage forms and are generally bulking agents. They are typically present in a weight concentration which is 1/2 to 2/3 of the concentration of the delivery system.

Useful solid diluents are microcrystalline cellulose products having particle sizes of about 20 micrometers (μm) to about 200 micrometers. The Avicel products, especially Avicel PH101 (FMC) are especially effective.

Disintegrants can be used to assist in the release of the active agent from the dosage form after the tablet has been ingested. Useful disintegrants include croscarmellose sodium, polyvinylpolypyrrolidone (PVPP), and sodium starch glycolate. Ac-Di-Sol, a croscarmellose sodium product made by FMC, is also very useful, as is Kollidon CL-M, a micronized crospovidone. Mixtures are operable.

One or more glidants such as starch, talc, lactose, stearates and colloidal silica can be used. Cab-o-sil M5, a brand of colloidal silica made by Cabot, is very useful.

Lubricants are used in the tablet compositions, among them stearic acid, adipic acid, fatty acid esters, talc, magnesium stearate, mineral oil and the like and mixtures thereof. Stearic acid powder, such as that made by Sherex Chemical Co., is highly effective.

Other conventional pharmaceutical dosage form additives may be employed. Ingredients such as colorants, flavors, taste-masking agents, flow control agents, perfumes and stabilizers can be included in minor amounts.

Table 1. Tablet Ingredients

INGREDIENT	BROAD RANGE (%)	NARROW RANGE (%)
Active System	40-80	53-63
Solid Diluent	15-55	30 - 40
Disintegrant	0.5-10	2 - 4
Glidant	0.2 - 5	1 - 3
Lubricant	0.2 - 5	1 - 3
Other Additives	0 - 10	0 - 5

Optionally, particles of the inventive delivery system may be coated, or encapsulated, with materials which alter such properties as stability, taste, appearance and the like, but not the rapid release properties. Such coatings typically contain one or more pharmaceutically acceptable polymers, *e.g.*, cellulosics.

Thermoform processing, and liquiflash processing in particular preferably involves providing the ingredients with a particle size of about 2 to about 500 microns, and preferably (for ibuprofen) about 5 microns. Grinding/milling may be

necessary as preliminary steps to prepare the active. The particles of active and solubilizer are then blended and used as a feedstock for a suitable thermoforming device wherein heat and centrifugal pressure conditions are controlled to effect morphological changes in the feedstock.

Inside the liquiflash thermoform device, the solubilizer particles of the feedstock lose their resistance to liquid flow and become "liquiform." In this state, the material is physically transformed from its original solid state, through a "liquid" state and back to a solid state instantaneously. During this process the particles are also acted upon by centrifugal force, or another shearing force, which force further adds to the "liquiform" condition and causes the solubilizer portion of the feedstock to, at least partially, encapsulate the solid particle of active.

U. S. Patents 5,445,769 and 5,458,823, and application Serial Nos. 08/330,412 and 08/874,215, set out the details of the liquiflash and flash flow processing.

The invention will now be described by way of example.

Example I
Ibuprofen Delivery System

Three kilograms micronized ibuprofen (IBP) and two kilograms milled Poloxamer 188 were added to a Stephan mixer in the following order: (1) one-half of the solubilizer, (2) all of the IBP, (3) the remaining portion of the solubilizer. The ingredients were mixed for about three minutes. This mixture was used as a feedstock, as follows:

The feedstock was fed to the 5-inch spinning head disclosed in U. S. Application Serial No. 08/874,215, filed June 13, 1997. The head speed was increased to 60Hz while the heating elements were raised to a temperature that produced liquiflash conditions (about 60°C to 75°C).

The spinning head forced the material through its orifices and the product was permitted to free fall a distance of from six to eight feet below the head. It consists of globules containing 60:40 IBP:solubilizer.

After solidifying thoroughly the delivery system material was milled using a No. 6 screen.

Once milled, the solid particles can be used as is, *e.g.*, in a sachet, or powder, delivery system. Alternatively, they can be used in liquid, gel, tablet or capsule forms. Solid dosage forms are very effective. Optionally, one or more coatings, such as aesthetic coating(s), taste-masking coating(s) or enteric coating(s), can be applied before the particles are used to deliver active agents to individuals.

Example II

Ibuprofen Dissolution Studies

A. 40:60 IBP/Poloxamer

Using a procedure similar to that of Example I, particles containing 40% IBP that had not been previously micronized and 60% milled Poloxamer 188 were produced. These spheres were subjected to dissolution testing using USP Method II in phosphate buffer adjusted to pH 6.0 (37° C).

The particles demonstrated the following dissolution properties in the pH 6 medium:

MINUTES	PERCENT DISSOLVED
5	92
10	96
20	96
45	95
60	95

B. 50:50 IBP/Poloxamer.

Using the procedure of Example I, particles of 50% micronized IBP and 50% milled Poloxamer 188 were made.

Using the testing method described in A, above, dissolution studies were run in pH 6.0 medium. The properties were:

MINUTES	PERCENT DISSOLVED*
5	102
10	102
20	102
45	102
60	101

*Calculated values

Example III

Ibuprofen Particle Studies

In bioavailability tests, particles of the inventive delivery system made in accordance with Example I gave faster times to maximum plasma concentration (T_{max}) than times obtained using a commercial IBP tablet (NUPRIN, Bristol-Myers Squibb Co.).

The tests were designed to determine IBP plasma concentrations at various points in time. Enhanced absorption of ibuprofen was seen at earlier time points, with individual subject plasma concentration time profiles given below. T_{max} was determined from the concentration data, and was found to be 1.10 hours for the particles and 1.38 hours for the commercial product.

Ten healthy male volunteers took part in a single dose, randomized crossover study. Plasma samples were collected pre dose and at 0.25, 0.5, 0.75, 1, 1,25, 1,5, 1,75, 2, 2.25, 2.5, 3, 4, 6, 8, 10 and 12 hours post-dose.

The following tables show individual subject plasma concentration-time profiles at early time points comparing the fast release delivery system and NUPRIN tablets.

	A. NUPRIN			B. Particles of the Invention	
Subject	0.25 hours	0.5 hours	Subject	0.25 hours	0.5 hours
1	0	15.4	1	10.4	14.5
2	0	7.31	2	9.24	13
3	0.418	7.31	3	7.64	11.5
4	3.53	9.88	4	5.82	9.28
5	8.74	22.2	5	6.65	14.5
6	0.250	2.34	6	6.09	11.8
7	2.73	5.63	7	6.15	11.8
8	0.29	4.43	8	0.914	6.2
9	3.65	8	9	10.3	20
10	1.78	10.8	10	16.7	19.9
Average	2.1397	9.33	Average	7.9904	13.248
SD	2.735264	5.787295	SD	4.113166	4.290661

Example IV

Ibuprofen Tablets

Tablets were prepared containing 58% of 60:40 ibuprofen:Pluronic F-68 particles; 35% Avicel PH101; 3% croscarmellose sodium; 2% Cab-o-sil and 2% Stearic acid. The ingredients were blended in a V-blender and compressed on a Killian T200 rotary tablet press using 8 x 16 mm caplet tooling.

Example V

Ibuprofen Tablet Dissolution Studies

200mg ibuprofen tablets containing 60:40 ibuprofen:solubilizer rapid release particle were subjected to dissolution testing using USP Method II, (50 rpm), phosphate buffer (900 ml, 37°C) adjusted to pH 5.2. They had the following dissolution profile:

TIME (MINUTES)	PERCENT DISSOLVED
5	77
10	86
20	89
30	91
45	92
60	92

For comparison, a dissolution study was run on 200 mg tablets of ADVIL, a commercially available preparation of Whitehall Labs (American Home Products Corp.).

Each tablet is believed to contain: ibuprofen, acetylated monoglyceride, beeswax and/or carnauba wax, croscarmellose sodium, iron oxides, lecithin, methylparaben, microcrystalline cellulose, pharmaceutical glaze, povidone, propylparaben, silicon dioxide, simethicone, sodium benzoate, sodium lauryl sulfate, starch, stearic acid, sucrose, and titanium dioxide. See page 828 of the Physician's Desk Reference for Non-prescription Drugs, 19th ed. (1998).

Using the same conditions as above, the ADVIL tablets had the following dissolution profile:

TIME (MINUTES)	PERCENT DISSOLVED
5	23
15	37
30	48
45	54
60	58

Clearly, the delivery system material containing the ibuprofen in the tablets of the invention dissolved faster than the commercial formulation. Seventy-seven percent (77%) of the ibuprofen in the particles was dissolved in 5 minutes, compared to 23% dissolution of ADVIL in the same time period.

Example VI

Ibuprofen Delivery System

A 60:40 weight ratio mixture of micronized ibuprofen and Pluronic® F68 was extruded in a MPV 2015, 15 mm twin screw co-rotating Baker Perkins extruder.

During the initial phase of processing, only the Pluronic® F68 surfactant was fed into the extruder. All four (4) temperature zones, namely barrel, die, and zone 2 and 3, were set at 73° C. Once a smooth extrudate flow was ensured, the 60:40 mixture was fed into the extruder. At this point the temperatures of the various zones were lowered to about 55° C. As the extrusion process continued, samples of the extrudate were collected on Teflon® coated flat trays at various time intervals from the start of the run. During this time the processing temperatures were dropped from about 55° C to about 42° C.

The extrusion process was run at an average rotational speed of about 31 rpm.

After completion of these runs, another set of runs was carried out with the same mix but extruded at the higher temperature of 80° C. The processing run continued for approximately 15 minutes during which three (3) sample were collected.

The samples collected were milled in a Braun coffee grinder and sieved through a 40 mesh sieve. These sieved samples were then subjected to dissolution testing using USP Method II in phosphate buffer adjusted to pH 5.2 (37° C). The percent dissolution of ibuprofen was measured at 5 minutes and the data summarized as follows:

Sample #	Die Temp. °C	Barrel Temp. °C	Barrel Melt Temp. °C	% Dissolution @ 5 minutes	Extrudate Clarity
1	38	39	42	73%	White
2	36	39	44	71%	White
3	43	43	46	77%	White
4	42	42	46	77%	White
5	44	44	48	75%	White
6	50	50	53	74%	White
7	54	54	56	70%	White
8	73	72	74	63%	Clear
9	66	73	78	45%	Clear
10	80	80	83	48%	Clear

Reasonable variations, such as those that would occur to a skilled artisan, can be made herein without departing from the scope of the invention.

WE CLAIM:

1. A thermoformed drug delivery system useful in making dosage forms having improved dissolution and shorter T_{max} for the drug consisting essentially of:

from about 50 to about 80% of an undissolved solid particulate form of at least one active agent in intimate contact with from about 20% to about 50% of a polymeric solubilizing agent(s) wherein the solid particulate active agent is generally soluble in a melt of the polymeric solubilizing agent.

2. The drug delivery system of claim 1 wherein the solubilizing agent is a diblock copolymer containing polyoxyethylene and polyoxypropylene units.

3. The drug delivery system of claim 2 wherein the at least one active agent is selected from the group consisting of H_2-antagonists, non-narcotic analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), anti-cholesterolemics, anti-allergy agents, anti-migraine agents and combinations thereof.

4. The drug delivery system of claim 3 wherein the active agent is ibuprofen.

5. The drug delivery system of claim 3 wherein the ratio of active agent to solubilizing agent is about 40:60.

6. The drug delivery system of claim 3 wherein the ratio of active agent to solubilizing agent is about 50:50.

7. The drug delivery system of claim 3 wherein the ratio of active to solubilizing agent is about 60:40.

8. A dosage unit comprising particles of the drug delivery system of claim 1, and one or more pharmaceutically acceptable excipients.

9. The dosage unit of claim 8 wherein the solubilizing agent is a diblock copolymer containing polyoxyethylene and polyoxypropylene units.

10. The dosage unit of claim 9 wherein the active is at least one agent selected from the group consisting of: H_2-antagonists, non-steroidal anti-inflammatory drugs (NSAIDs), non-narcotic analgesics, anti-cholesterolemics, anti-allergy agents, anti-migraine agents and combinations thereof.

11. The dosage unit of claim 10 wherein active is ibuprofen.

12. The dosage unit of claim 11 wherein the active has improved dissolution properties and a shorter T_{max}.

13. The dosage unit of claim 12 which is a tablet containing ibuprofen and a solubilizing agent wherein the ratio of ibuprofen to solubilizing agent is from about 60:40 to 80:20.

INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/US 98/20266

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/16 A61K31/19

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SMITH, A. ET AL: "The filling of molten ibuprofen into hard gelatin capsules" INT. J. PHARM. (1990), 59(2), 115-19 CODEN: IJPHDE;ISSN: 0378-5173, XP002093630 see page 117; table 3 ---	1-13
X	HAWLEY, A. R. ET AL: "Physical and chemical characterization of thermosoftened bases for molten filled hard gelatin capsule formulations" DRUG DEV. IND. PHARM. (1992), 18(16), 1719-39 CODEN: DDIPD8;ISSN: 0363-9045, XP002093631 see page 1724 --- -/--	1-13

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 February 1999	02/03/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Boulois, D

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/US 98/20266

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 413 171 A (DOLORGIET GMBH & CO KG) 20 February 1991 see page 2, line 25 - line 32 see page 3, line 11 - line 14	1-13
X	WO 93 25190 A (STERLING WINTHROP INC) 23 December 1993 see page 6, line 25 - line 31 see page 9, line 17 - line 27 see page 16 - page 17; example 3	1-13
X	GB 1 388 786 A (SCHERER CORP R P) 26 March 1975 see page 3, line 40 - line 114 see page 5 - page 6; examples 6,7 see page 1, line 11 - line 24	1,5-8, 12,13
X	US 5 501 858 A (FUISZ RICHARD C) 26 March 1996 see column 2, line 34 - line 42 see column 6 - column 7; example 2	1,3,5-8, 10,12,13
X	WO 97 02017 A (ELAN CORP PLC ;CLANCY MAURICE JOSEPH ANTHONY (IE); CUMMING KENNETH) 23 January 1997 cited in the application see page 5, line 20 - line 26 see page 6, line 11 see page 16 - page 17; example 2	1-3, 5-10,12, 13
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A	EP 0 709 086 A (FUISZ TECHNOLOGIES LTD) 1 May 1996 cited in the application see page 14; example 4	1-13

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/ 20266

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
See FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: 1

In view of the large number of compounds which are theorically defined by the expression "active agent" and "a polymeric solubilizing agent" in Claim 1, the search has been restricted for economic reasons. The search was limited to the general concepts of "active agent" and "a polymeric solubilizing agent", to the compounds cited in claims 2,3,9,10 and in the description on page 5 line 4- page 6, line 3, in the examples, and to the relevant IPC groups concerned (PCT Search Guidelines PCT/GL2, Chapter III, 2.1., 3.6. and 3.7.; see Rule 33(3) PCT).

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interi ıal Application No
PCT/US 98/20266

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